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Current Indications for Percutaneous Coronary Intervention for Chronic Stable Angina: Implications of the COURAGE Trial

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Patients presenting with symptoms of chronic stable angina represent a relatively significant portion of general population, especially among older aged. Among people 45-54 years old, stable angina is reported between 2-5% in men and 0.5-1% in women, while among people 65-74 years old the corresponding incidence is reported 11-20% for men and 10-14% for women respectively. In >50% of these patients angina limits significantly everyday activities leading to premature retirement, according to various national health and insurance surveys.

Chronic stable angina is a slowly progressive disease and the patients show a relative mortality of approximately 2% per year, significantly lower than the mortality of patients with unstable acute coronary syndromes or vascular disease and only slightly higher than that of patients with several risk factors who are under treatment for primary prevention. Mortality among patients with stable angina is related to the extension and the severity of coronary artery disease (CAD), their left ventricular function, exercise capacity, nature of the symptoms and ECG findings both at rest and during stress.

The main objectives of the treatment of patients with chronic stable angina, as outlined in the current guidelines, are directed towards preventing myocardial infarction and death (thereby improving the "quantity" of life) as well as preventing further ischemia and related symptoms (thereby improving "quality" of life) [1]. Current stable angina treatment includes medical therapy, percutaneous coronary revascularization procedures (PCI) and surgical revascularization (CABG). A meta-analysis of six randomized trials of percutaneous coronary revascularization with plain old balloon angioplasty (POBA) showed that, compared to medical treatment, POBA offered more symptomatic relief in patients with stable angina, without any significant difference in the rate of death, acute MI or need for new PCI. There was only a trend for more CABG procedures among patients treated with POBA and this was attributed to an excess of ischemic complications [2]. It must be mentioned that recent technical advances such as stents or newer devices that could improve the efficacy of POBA and abolish this excess have not been used in these trials.

In another meta-analysis [3] of 11 randomized trials of PCI with implantation of bare metal stents (BMS), treatment of patients with stable angina by PCI showed no difference in death, acute myocardial infarction (MI), CABG or PCI procedures compared to medical treatment. Common finding in all these trials is that PCI shows no difference in death or MI compared to medical therapy, but a clear and sustained benefit in angina relief. As it is underscored also in MASS II trial results, neither PCI

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nor CABG have ever been shown to improve the already excellent survival of most patients with stable CAD treated with medical therapy and the main indication for revascularization of stable CAD patients is angina relief and restored quality of life [4]. As a consequence, in 2006 the American Heart Association as well as the European Society of Cardiology issued the current guidelines for the treatment of patients with stable angina. According to these guidelines, "revascularization in patients with angina CCS class I to IV despite medical therapy is a class IA recommendation and can be performed either by PCI, irrespectively of the extension of underlying CAD (especially in non diabetics) or by CABG, in cases of left main or three vessel disease and objective large ischemia. Either PCI or surgery may be considered as an effective option for treatment of symptoms of these patients. Single or multivessel PCI can be performed with high success using stents, drug eluting or not, and the risk of death is estimated 0.3-1%. Compared with medical therapy, PCI does not provide survival benefit in stable angina but is more effective at reducing events that impair quality of life. Initial pharmacological approach may be taken in patients not at high risk and revascularization may be recommended for patients with suitable anatomy who do not respond adequately to medical treatment or those who wish to remain physically active".

Last year the results of the COURAGE trial were published in the New England Journal of Medicine, producing one of the biggest debates concerning the value of PCI in the treatment of patients with stable angina [5]. In this trial an hypothesis was tested, that PCI plus optimal medical therapy would be superior to optimal medical therapy alone. The primary end point of the study was death or non fatal MI, opposite to all up to now existing data that have shown no influence of either method to hard clinical end points. Secondary end points of the study were death, MI or stroke, new hospitalization for acute coronary syndrome, quality of life including angina and cost effectiveness.

This trial was performed in the USA and Canada and 2287 patients were enrolled in it, mainly (83%) in USA Veterans or Canadian Hospitals usually not performing PCI or with a very low PCI volume. The 2287 patients enrolled was only a small percentage (6%) of the total 35539 patients screened for the study. The main reasons for exclusion from the study were class IV angina, failed medical therapy, low left ventricular ejection fraction, recent revascularization procedure, left main disease or not suitable anatomy, co-existing illness, complications of acute MI, restenosis post PCI, etc. This means that almost all the patients with high risk features who would gain benefit from revascularization were excluded and the remaining included population had a low annual risk of death, less than 1%. In this highly selected and relatively low risk population the hypothesis of the trial tested, opposite to all existing data, seems to be unreal.

Patients were randomized to a optimal medical therapy (OMT) with all the available pharmacologic agents along with regular weekly activity or to PCI plus optimal medical therapy (PCI+OMT). All patients, at five years follow up, found to be very compliant to the assigned medical therapy with levels of LDL cholesterol around 70 mg%, HDL cholesterol around 40 mg%, normal blood pressure and regular moderate weekly activity (5x/week).

On the contrary, PCI treatment was not optimal, in fact it was substandard. Patients were treated in low PCI volume hospitals and by less experienced interventionists. From the total number of patients assigned to invasive treatment, PCI was performed in 94% of them and was successful in only 93% of the PCI cases (a percentage significantly smaller than the success rate achieved contemporarily in most experienced centers throughout the world). Stents were used in 86% of the cases and most of them (97%) were bare metal stents, which show greater restenosis rate and consequently relapse of symptoms and more adverse events than the new more effective in reducing post PCI major adverse cardiac events (MACE) drug eluting stents (DES), which were used in only 3% of the patients. Around 47% of the patients with multivessel disease (371 out of 787) had incomplete revascularization, which has been correlated with less favourable outcome post PCI and even higher mortality rate. Finally, few patients received periprocedural infusion of platelet glucoprotein (Gp) IIb/IIIa inhibitors or adequate clopidogrel pre-loading, which has contributed in reducing periprocedural ischemic complications.

According to the results of the study, total mortality rate during 5 year follow up was found 7.6% for the PCI group and 8.3% for OMT group (hazard ratio: 0.87, p=0.38). Since total mortality was used as the primary end point of the study and half (53%) of the total 180 deaths reported were non cardiac, it seems that the selection of all cause mortality was not accurate because PCI would only be expected to reduce cardiac deaths. Despite that, PCI treatment was correlated with a non significant reduction of total death rate.

The 5-year survival free of death from any cause and MI did not differ among the two groups of patients (hazard ratio: 1.05, p=0.62). As far as MI rate (any biomarker elevation) at 5 years, it was found a little higher in the PCI group (13.2% versus 12.3% in OMT group) with a hazard ratio: 1.13, p=0.33. Nevertheless, it should be mentioned that spontaneous MI rates during follow up period were higher in the OMT group (119 versus 108 in PCI) and the total difference observed was due to more periprocedural MIs seen in the PCI group (35 versus 9 in OMT) attributed to the lack of adequate antiplatelet regimen used.

Considering the "hard" clinical end points of the study, PCI treatment versus OMT was found more effective in reducing non significantly death by 13% (7.6% vs 8.3%), spontaneous MI by 11% (9.3% vs 10.4%) and highly significantly the revascularization rate by 40% (21.6% vs 31,6%, p<0.001). A

percentage of 74% of the PCI and 72% of the OMT patients were angina free at 5 years follow up, but if we consider the 10% more patients of the OMT group crossing over to PCI, the difference of angina-free patients is quite significant at 5 years (74% versus 62%) in favour of PCI treatment. Patients of the PCI group also compared to OMT used significantly less antianginal medication, such as nitrates or calcium blockers, during long term follow up.

From the above mentioned data it is quite obvious that the COURAGE trial, in accordance with all the previous well conducted studies, showed that compared to optimal medical therapy, PCI performed in patients with stable CAD offers no difference in mortality or MI rate but a great benefit in quality of life with less medication use and lower repeat revascularization rate [6].

Recently the results of the nuclear substudy of the COURAGE trial have been published [7]. In this study myocardial ischemia reduction, evaluated by myocardial perfusion scintigraphy, was examined among patients pre and at a mean of 12 months post treatment with PCI or OMT. Patients allocated to PCI showed a mean reduction by 2.7% of ischemic myocardium, while patients on OMT showed a modest reduction of only 0.5% of ischemic myocardium ($p<0.0001$). A percentage of 33% of patients treated by PCI showed ischemia reduction in ≥5% of myocardium while only 19% of patients treated with OMT showed the same reduction ($p=0.004$). These new findings further support the use of PCI in the treatment of patients with stable CAD for improvement of their functional status and reduction of ischemic complications.

In ***conclusion,*** current valid evidence-based medicine guidelines in stable CAD propose PCI for better control of angina and improvement of functional status especially when DES are used. It is appropriate to treat patients without high risk noninvasive testing with anti-anginal therapy first and then refer those who fail medical therapy for assessment of myocardium at risk and eventual PCI. ***Post COURAGE trial nothing has changed.*** All high risk patients or patients with symptoms despite optimal medical therapy and suitable coronary anatomy should undergo PCI. Patients who should not receive PCI today are the patients with no angina, no ischemia, no stenosis (because treatment of vulnerable plaque remains an unproven concept) or no hope.

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